REMARKS

Drawings

The Examiner states that Figs. 4, 5, 6, and 8 are not acceptable because the drawings are illegible.

A set of clean copies of Figs. 4, 5, 6, and 8 are provided herein. Withdrawal of the objections to the drawings are respectfully requested.

Claim Rejections – 35 USC §112, First Paragraph

Claims 4 to 15 have been rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To address this rejection, the preamble of the claims has been amended to incorporate claim 9 to state, "An electrophoresis gel containing two-dimensional genomic DNA data pattern."

Claim 7 has been amended and incorporated into other claims to obviate the lack of written description rejection.

Claim Rejections – 35 USC §112, Second Paragraph

Claims 4 to 15 have been rejected as being indefinite.

The preamble has been amended to address this rejection. Other indefinite rejections have been address by the amendment provided herein.

Claim Rejections – 35 USC §102

Claims 4, 5, and10 have been rejected as being anticipated by Belyavsky et al.

Belyavsky et al. discloses dividing the biotinylized fragments into subsets with the aid of immobilization on a solid support (see Fig. 1 and column 4 line 66 to column 5, line 3) while, in contrast, the present invention does not anchor the DNA fragments to any solid support to derive the subset but selectively labels the ends with specific adapters to select the fragments. To reflect this difference, claims 4 and 10 have been amended to combine with claim 7 to emphasize that the ends are labeled with specific adapters and not immobilized.

Claims 4 to 6 and 12 to 15 have been rejected as being anticipated by Hatada et al.

Hatada et al. does not teach an eletrophoresis gel obtained by using adapters that can recognize a complementary restricted cleavage site as defined in claims 4 and 12. The resultant difference in the electrophoresis gel is readily apparent by looking at Figs. 7 and 8. Indeed, the electrophoresis gel of the present invention would be very different from the electrophoresis gel obtained by RLGS. Thus, claims 4 to 6 and 12 to 15 are not anticipated by Hatada et al. (see more on Hatada et al. below).

Claims 4 to 5 and 10 to 11 have been rejected as being anticipated by Hayashizaki et al.

Hayashizaki et al. does not teach an electrophoresis gel obtained by using adapters as above. Therefore, claims 4 to 6 and 12 to 15 are not anticipated by Hayashizaki et al. (see more on Hayashizaki et al. below).

Claim Rejections – 35 USC §103

Claims 4, 5, 6, 12, 13, and 15 have been rejected as being unpatentable overe Hatada et al. in view of Carrano et al.

Claims 4, 5, 6, 10, and 11 have been rejected as being unpatentable over Hyayshizaki et al. in view of Carrano et al.

Claim 4 recites:

> 4. (Currently Amended) An electrophoresis gel containing two-dimensional genomic DNA data pattern obtained by a method comprising:

(a) treating genomic DNA with a first restriction enzyme that provides 3'-protruding end cleavage sites of different sequences;

(b) linking one end of an adapter to a restriction enzyme cleavage site, which was cut by the first restriction enzyme and is complementary to the end of the adapter, and labeling the other end of said adapter;

(c) treating the resulting DNA fragments with a second restriction enzyme and subjecting the resultant restricted fragments to electrophoresis to bring about a first-dimensional fractionation; and

(d) treating the fractionated DNA fragments of step (c) with a third restriction enzyme and subjecting the resultant restricted, fractionated fragments to electrophoresis to bring about a second-dimensional fractionation,

wherein the first restriction enzyme comprises a recognition sequence that includes Ns, where each N can be any of A, G, C, or T and the linking end of the adapter having a ligating sequence is designed to anneal to the restriction enzyme cleavage site and has a base complementary to each N in the recognition sequence of the first restriction enzyme.

The present invention as claimed uses 3'-protruding end cleavage site to attach the adapters. This is very distinct from Hatada et al. in that Hatada et al.'s restriction landmark genomic scanning (RLGS) method employs "(i) direct end labeling of the genomic DNA digested with a restriction enzyme and (ii) high-resolution, two-dimensional electrophoresis." (Page 9523, first complete paragraph from the bottom of the first column.) **Hatada et al.'s method involves labeling all the cleaved ends at both ends of each fragment (see Fig. 1) without any adapters attached to the ends. That is, <u>all the fragments are labeled</u>. In contrast, the present invention avoids labeling the restriction sites themselves by creating restriction cleavage sits having 3'-protruding ends. It is done this way because the 3'-protruding end cannot be labeled by Sequenase.** Labeling both ends of each fragment as opposed to selectively labeling with adapters results in a very different electrophoresis gel.

Furthermore, Carrano et al. uses "a single stranded oligonucleotide primer with a fluorochorme covalently bound to its 5'-end is annealed to a synthetic oligonucleotide to create a double-stranded oligonucleotide linker with a **5'-overhang** complementary to a restriction enzyme site." (Page 129, first column, lines 3 to 8; see also Fig. 1.) (Emphasis added.) This means that the restricted site in Carrano et al. has a 5'-overhang. In the present invention, the restricted cleavage site has a 3'-protruding end to combine with an adapter with a 3'-overhang. The 3'-protruding end is created to avoid labeling cleavage sites without the adapters. The

present invention requires that the adapters bind to the 3'-protruding end of the fragment and the labels only bind to the adapaters. Thus, even if Carrano et al. is combined with Hatada et al., a person of ordinary skill in the art would not have been able produce the presently claimed invention. Thus, claims 4, 5, 6, 12, 13, and 15 would not have been obvious at least for this reason. Note that claim 12 originally included the "3'-protruding end" feature.

Moreover, the Examiner combines Carrano et al. with Hatada to allege that using the adapters would have been obvious. However, why would a person of ordinary skill in the art use adapters to the RLGS method when Hatada et al. does not espouse using adapters but teaches directly labeling the restricted cleavage site? The reason why Hatada et al. does not use adapters is that RLGS was invented to landmark all the restricted cleavage sites. A use of adapters (as claimed by the present invention) would necessarily impede labeling the restricted cleavage sites because some would be labeled by the adapter but some would not, and therefore, would run counter to the objective of Hatada et al.'s RLGS method. There is no teaching, suggestion, or motivation in either Hatada et al. or Carrano et al. to use adapters with the RLGS method. Thus, a person of ordinary skill in the art would not have looked to Carrano et al. to use adapters in Hatada et al. because the use of adapters would necessarily impede the very objective of the RLGS method.

Hayashizaki et al. also is same as Hatada et al. in that all the cleaved ends are labeled without the use of adapters. (See Fig. 2). The above arguments apply equally to Hayashizaki in view of Carrano et al.

Claims 7, 8, and 9 have been rejected as being unpatentable over Hatada et al. in view of Carrano et al. as applied to claims 4, 5, 6, 12, 13, and 15, and further in view of the New England Biolabs Catalog.

Claim 8 (claims 7 and 9 canceled), which depends on claim 4, would not have been obvious for the reasons given for Hatada et al. in view of Carrano et al. Note that Carrano et al. teaches using restriction enzymes that leave 5'-overhangs. Thus, the teaching of the cited prior art would direct a person of ordinary skill in the art not to the enzymes claimed in claim 8 but to

different enzymes that leave 5' overhangs in the cleavage sites. Thus, Hatada et al. in view of Carrano et al. and further in view of the New England Biolabs Catalog would not have taught or suggested claim 8 or new claim 16 or any other claims.